Synthesis and Reactivity of 6α-Methoxy-2-methyl-6β-phenoxyacetamidopenem-3-carboxylates

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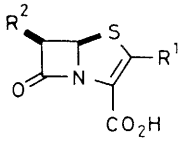
Representatives of the title compounds have been prepared from phenoxymethylpenicillinic acid; the β-lactam linkage of these compounds is exceptionally reactive.

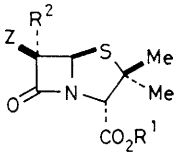
Penem-3-carboxylic acid derivatives are of considerable current interest because simple representatives, *e.g.* (**1a**, **b**)[1,2] display potent antibacterial activity. Following the report that acids (**1c**, **d**) possessed only weak antibacterial properties,[3] little attention has been devoted to the synthesis of 6-acylaminopenems.[4–6] The dramatic difference in biological activity of penems (**1a**, **b**) and (**1c**, **d**) is probably a reflection of the relative chemical stability of these compounds; thus, whereas penem (**1b**) showed a half life of 20 h at pH 7.4,[7] penems (**1c**, **d**) underwent spontaneous decomposition.[3] In the case of penicillins, it has been shown that the introduction of a methoxy-group at the 6α-site reduces the chemical reactivity of the β-lactam linkage; for example, compound (**2b**) underwent hydrolysis, at pH 10, 3.3 times slower than compound (**2a**).[8] In the hope of reducing the chemical reactivity of 6β-acylaminopenems, we have prepared the first representatives of 6β-acylamino-6α-methoxypenems. Preliminary studies suggest that these compounds show greater chemical reactivity than their 6α-unsubstituted counterparts.

Our decision to use Woodward's strategy[3] for the construction of penems of type (**3**) required access to thioesters of type (**4**). After examining several routes, we found that sulphoxides of type (**5**) [readily prepared from penicillinates of type (**6**) by a modified Koppel–Koehler procedure][9] were the most satisfactory precursors. Treatment of penicillinate (**6a**) in tetrahydrofuran–methanol at −75 °C with t-butyl hypochlorite (1.3 mol. equiv.) followed by methanolic lithium methoxide (3.5 mol. equiv.) (15 min at −70 °C and 20 min at −50 °C) gave, following work-up (quenching with $MeCO_2H$ and Zn dust), the 6α-methoxy-derivative (**5a**) (60% after SiO_2 chromatography). The sulphoxide (**5a**) was heated in a 5:1 mixture of toluene–acetic anhydride in the presence of triethyl phosphite[10] (2 mol. equiv.) for 4 h and the crude



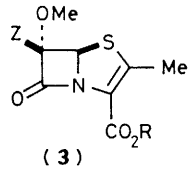
(1)

a; R^1 = Me, R^2 = H
b; R^1 = R^2 = H
c; R^1 = Me, R^2 = PhO.CH_2.CO.NH
d; R^1 = H, R^2 = PhO.CH_2.CO.NH



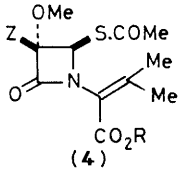
(2)

a; R^1 = R^2 = H
b; R^1 = H, R^2 = OMe
c; R^1 = Me, R^2 = H
d; R^1 = K, R^2 = H
e; R^1 = CH_2.COMe, R^2 = H
f; R^1 = Na, R^2 = H



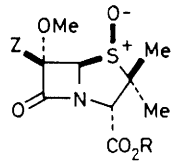
(3)

a; R = Me
b; R = Na
c; R = H
d; R = CH_2.COMe
e; R = *p*-NO_2.C_6H_4.CH_2



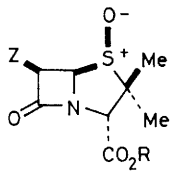
(4)

a; R = Me
b; R = CH_2.CO.Me
c; R = *p*-NO_2.C_6H_4.CH_2



(5)

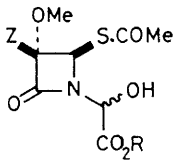
a; R = Me
b; R = CH_2.COMe
c; R = Na
d; R = H



(6)

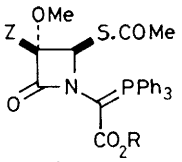
a; R = Me
b; R = CH_2.COMe

Z = PhO.CH_2.CO.NH–



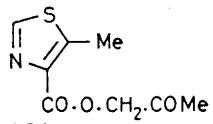
(7)

a; R = Me
b; R = *p*-NO_2.C_6H_4.CH_2

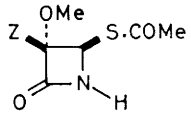


(8)

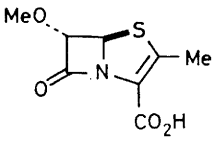
a; R = Me
b; R = CH_2.COMe
c; R = *p*-NO_2.C_6H_4.CH_2



(9)



(10)



(11)

product was then treated with triethylamine in ethyl acetate; following silica gel chromatography, the thioester (**4a**), $[\alpha]_D$ +51° ($CHCl_3$), was isolated in 50% yield.

Reductive ozonolysis of butenoate (**4a**) (O_3 in CH_2Cl_2 at −70 °C, addition of $MeCO_2H$–Zn, warming to room temperature) gave the substituted amide (**7a**) as a 1:1 mixture of diastereoisomers, in quantitative yield. Sequential treatment of compound (**7a**) with 2,6-lutidine (1.2 mol. equiv.) and thionyl chloride (1.1 mol. equiv.) in tetrahydrofuran (−30 °C → 0 °C, filtration, evaporation) and triphenylphosphine (2 mol. equiv.) and silica gel (10 mass equiv.) in tetrahydrofuran was followed by evaporation. After 15 h the mixture was loaded onto a silica gel column; elution gave phosphorane (**8a**) (60%), m.p. 87—90 °C, $[\alpha]_D$ +33° ($CHCl_3$).

When heated (*ca.* 83 °C, 4 h) in toluene containing hydroquinone under nitrogen, phosphorane (**8a**) was converted into penem (**3a**) (52%), $[\alpha]_D$ +323° ($CHCl_3$).

Having established that penem (**3a**) was isolable, efforts were made to prepare salt (**3b**) and/or acid (**3c**). Since Woodward had shown that the sodium salt of penem (**1a**) was readily derivable from its acetonyl ester,[7] the synthesis of penem (**3d**) was undertaken. This was achieved from penicillinate (**6b**) using the aforementioned reaction sequence.

Sulphoxide (**6b**), m.p. 135—136 °C, $[\alpha]_D$ +187° ($CHCl_3$), prepared (88%) from potassium phenoxymethylpenicillinate (**2d**) by sequential reactions with chloroacetone and sodium periodate, was converted *via* 6α-methoxy-derivative (**5b**), $[\alpha]_D$ +281° ($CHCl_3$), into thioester (**4b**) [41% based upon (**6b**)], m.p. 101—102 °C, $[\alpha]_D$ +60° ($CHCl_3$). Phosphorane (**8b**), $[\alpha]_D$ +32° ($CHCl_3$), obtained from the butenoate (**4b**) in 34% overall yield, gave penem (**3d**) (57%), m.p. 117 °C, $[\alpha]_D$ +351° ($CHCl_3$), when heated (20 h at 83 °C and 9 h at 93 °C) in toluene.

In a 1.5:1 mixture of acetonitrile–water, acetonyl esters (**2e**) and (**5b**) reacted with 0.1 M sodium hydroxide (1 mol. equiv.) to give salts (**2f**) and (**5c**); following acidification, acids (**2a**) and (**5d**) were isolated in respective yields of 62 and 78%. Under corresponding conditions, acetonyl ester (**3d**) reacted with sodium hydroxide to give thiazole (**9**) (80%). Evidently, in penem (**3d**), the β-lactam carbonyl group is preferentially attacked by sodium hydroxide. Penem (**3d**) showed a half-life of *ca.* 40 min at pH 7.4 and of *ca.* 258 min at pH 4.0 at 20 °C.

In the hope that it would serve as a precursor of acid (**3c**), the synthesis of *p*-nitrobenzyl ester (**3e**) was undertaken. Since attempts to convert butenoate (**4c**) into amide (**7b**), by reductive ozonolysis, were unrewarding, efforts were directed towards the derivation of azetidinone (**10**). Unfortunately, application of the usual ozonolysis–methanolysis procedure to butenoate (**4a**) failed to give azetidinone (**10**). Oxidation of butenoate (**4a**) with potassium permanganate[11] provided compound (**10**), m.p. 136—139 °C, $[\alpha]_D$ +72° ($CHCl_3$), albeit in low yield (*ca.* 15%). Sequential treatment of azetidinone (**10**) with *p*-nitrobenzyl glyoxylate–triethylamine, 2,6-lutidine–thionyl chloride, and triphenylphosphine–silica gel gave phosphorane (**8c**), which was transformed into penem (**3e**) [20% based upon (**10**)], m.p. 152—153 °C, $[\alpha]_D$ +276° ($CHCl_3$), when heated in toluene (11 h at 95 °C).

An attempt to convert *p*-nitrobenzyl ester (**3e**) into acid (**3c**), using the conditions that were successful for deriving acids (**1c, d**)[3] and (**11**)[12] from the corresponding *p*-nitrobenzyl esters, led to the isolation of non-β-lactam material. Presumably, the acid (**3e**) is inherently less stable than its counterparts (**1c, d**) and (**11**).

On the basis of the aforementioned results, it is clear that

replacement of the hydrogen atom at the 6α-position by the methoxy-group confers no increased stability upon 6β-acylaminopenems.

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